

Cancer immunotherapy

Koh, Sarene; Bertoletti, Antonio

DOI:

[10.1016/j.jhep.2014.06.023](https://doi.org/10.1016/j.jhep.2014.06.023)

License:

Other (please specify with Rights Statement)

Document Version

Peer reviewed version

Citation for published version (Harvard):

Koh, S & Bertoletti, A 2014, 'Cancer immunotherapy: Targeting the difference', *Journal of Hepatology*, vol. 61, no. 5, pp. 1175-1177. <https://doi.org/10.1016/j.jhep.2014.06.023>

[Link to publication on Research at Birmingham portal](#)

Publisher Rights Statement:

NOTICE: this is the author's version of a work that was accepted for publication in *Journal of Hepatology*. Changes resulting from the publishing process, such as peer review, editing, corrections, structural formatting, and other quality control mechanisms may not be reflected in this document. Changes may have been made to this work since it was submitted for publication. A definitive version was subsequently published in *Journal of Hepatology*, Vol 61, Issue 5, November 2014, DOI: 10.1016/j.jhep.2014.06.023.

Eligibility for repository checked February 2015

General rights

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

- Users may freely distribute the URL that is used to identify this publication.
- Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
- User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)
- Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

Take down policy

While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact UBIRA@lists.bham.ac.uk providing details and we will remove access to the work immediately and investigate.

Accepted Manuscript

International hepatology

Cancer Immunotherapy: Targeting the difference

Sarene Koh, Antonio Bertolotti

PII: S0168-8278(14)00453-X

DOI: <http://dx.doi.org/10.1016/j.jhep.2014.06.023>

Reference: JHEPAT 5225

To appear in: *Journal of Hepatology*

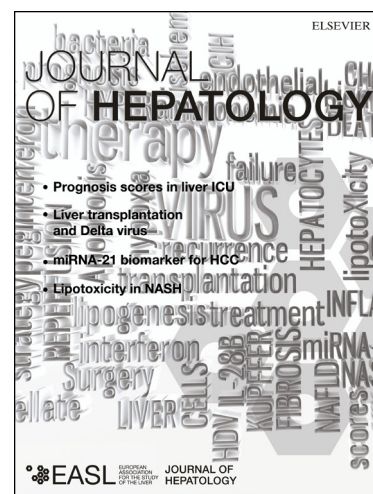
Received Date: 5 June 2014

Revised Date: 19 June 2014

Accepted Date: 19 June 2014

Please cite this article as: Koh, S., Bertolotti, A., Cancer Immunotherapy: Targeting the difference, *Journal of Hepatology* (2014), doi: <http://dx.doi.org/10.1016/j.jhep.2014.06.023>

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.



Cancer Immunotherapy: Targeting the differenceSarene Koh¹, Antonio Bertoletti^{1,2,3}¹*Viral Hepatitis Laboratory, Singapore Institute for Clinical Sciences, A*STAR, Singapore.*²*Program Emerging Infectious Diseases, Duke-NUS Graduate Medical School, Singapore.*³*School of Immunity and Infection, College of Medical and Dental Science, University of Birmingham, Edgbaston Birmingham, UK*

Keywords: cancer, immunotherapy, tumor infiltrating lymphocytes

*Corresponding author: Address: Emerging Infectious Diseases, Duke-NUS Graduate Medical School, 8 College Road, Singapore 169857. Tel.: +65 66013574.
 E-mail address: antonio@duke-nus.edu.sg (A. Bertoletti)

COMMENTARY ON:

Cancer Immunotherapy Based on Mutation-Specific CD4+ T Cells in a Patient with Epithelial Cancer. Tran E, Turcotte S, Gros A, Robbins PF, Lu YC, Dudley ME, Wunderlich JR, Somerville RP, Hogan K, Hinrichs CS, Parkhurst MR, Yang JC, Rosenberg SA. Science. 2014 May 9;344(6184):641-645. Reprinted with permission from AAAS.

<http://www.ncbi.nlm.nih.gov/pubmed/24812403>

Abstract. *Limited evidence exists that humans mount a mutation-specific T cell response to epithelial cancers. We used a whole-exomic-sequencing-based approach to demonstrate that tumor-infiltrating lymphocytes (TIL) from a patient with metastatic cholangiocarcinoma contained CD4+ T helper 1 (TH1) cells recognizing a*

mutation in erbb2 interacting protein (ERBB2IP) expressed by the cancer. After adoptive transfer of TIL containing about 25% mutation-specific polyfunctional TH1 cells, the patient achieved a decrease in target lesions with prolonged stabilization of disease. Upon disease progression, the patient was retreated with a >95% pure population of mutation-reactive TH1 cells and again experienced tumor regression. These results provide evidence that a CD4+ T cell response against a mutated antigen can be harnessed to mediate regression of a metastatic epithelial cancer.

T cell based cancer immunotherapy, the concept of utilizing T cells to cure cancer patients was until recently regarded with skepticism. One of the main conceptual problem is that, physiologically, T cells recognize and eliminate cells that express non-self proteins. These are not usually present in cancer cells that instead express so called “tumor-associated antigens”, which are self-antigens expressed at different levels in cancer versus normal cells [1,2]. There are immunological consequences of this feature: tumor-associated antigens are poor inducers of tumor-specific T cells that do not expand in patients or poorly recognized the tumor cells. A second consequence is that if and when tumor-associated antigen-specific T cells are efficiently produced (for example by engineering T cells with chimeric T cell receptor (TCR) specific for tumor-associated antigens), the T cells will not only target tumor but also normal cells with clinical outcome that might be extremely severe [3]. However, the concept that cancerous cells do not express immunogenic non-self antigens change after the demonstration that the genetic alterations present in cancers can lead to production of new immunogenic “non-self” antigens that can be exploited to induce effective tumor-specific T cell response. T cells specific for these

tumor-specific neo-antigens were detected in melanoma and were suggested to be the cause of the high immunogenicity of this cancer.

In this new paper, Tran *et al.*, makes the very important demonstration that such “neo antigens” are present and immunogenic not only in melanoma but also in cancer of epithelial origin which account for 80% of all human cancers. Furthermore, they not only demonstrated that T cell recognizing a mutated version of a tumor associated antigen can be detected in a patient with metastatic cholangiocarcinoma but also that these mutation-specific T cells unique to the patient’s cancer can be harnessed to mediate regression of a metastatic epithelial cancer.

To demonstrate the presence of the mutation-specific T cells, the authors first used a leading-edge whole-exomic sequencing based approach to identify mutated candidate epitopes expressed on lung metastases of a patient with bile duct cancer not responsive to standard chemotherapy. The 26 detected mutated sequences were expressed on autologous antigen presenting cells using constructed libraries of minigenes encoding the mutated sequences. They then tested whether the patient’s tumor-infiltrating lymphocytes (TIL) recognized any of these mutations and demonstrated that T cells infiltrating the patient’s tumor comprised of T cells that recognized only a mutated version of a ERBB2-interacting protein (ERBB2IP) but were unresponsive to the wild type non-mutated ERBB2IP. These mutations-specific T cells were CD4 cells, HLA-DQB1*0601 restricted, recognized a minimal epitope composed of 13 amino acids and seemed to be of mono-oligoclonal origin since they were characterized for a very restricted TCR usage. Direct evidences that these mutation-specific T cells can be exploited for therapeutic purpose were obtained by showing that adoptive cell transfer of a large quantity (42.4 billion) of the expanded TIL, of which about 25% were CD4+ ERBB2IP mutation-reactive T lymphocytes

caused tumor regression and disease stabilization for approximately one year. This clinical efficacy was confirmed after a second round of adoptive T cell therapy in which 95% of the transferred cells were V β 22+ ERBB2IP mutation-reactive TH1 cells that caused an accelerated tumor regression.

Therefore, by demonstrating that mutations present in epithelial tumors produced new antigens able to induce T cells that recognize the patient-specific mutated protein, Tran *et al*/bring to the forefront an alternative strategy to generate T cells for adoptive cell therapy and treat patients with common epithelial cancers, where there is a low frequency of tumor-reactive T cells. The results presented in this study are also encouraging as CD4+ TH1 cells, other than CD8 CTL, can confer clinical benefit in targeting cancer.

Targeting sporadic or driver mutations unique to a patient's individual cancer with mutation-reactive T cells have also the advantage to cause minimal amount of "off-target" reactivity (cross-reactivity) and thus avoiding the severe side effects that have been described in some recent cancer immunotherapy trials [4,5].

Despite the remarkable results, the data has been obtained from a single patient and the feasibility of such method have to be evaluated in more patients with different epithelial cancers to analyze the extent to which tumor mutations can be targeted by adoptive T cell therapy. Furthermore, the approach described in this report is perhaps limited to cancers where there are few mutations, as screening hundreds of mutations for immunogenicity is technically challenging with current technology and there is also the risk that an already genetically unstable tumor might simply escape immune attack via down-regulation of the target protein. There have been evidence in human studies suggesting that effective immunotherapy might lead to cancer immunoediting [6,7]. Given the heterogeneity of majority of cancers, it is difficult to

predict if targeting a single mutation epitope might result in durable tumor control or selection of immunoresistant tumor variants that might accelerate tumor progression [8]. Nevertheless, the authors commented that “mapping of the mutational landscape of human cancer is occurring at rapid pace but clinical strategies to exploit such knowledge for clinical benefit remains to be realized”; and perhaps in the near future it might be possible to apply multi-epitope-based cancer immunotherapies in the clinic.

This pioneering work opens the new exciting possibility to develop real personalized immune based targeted therapy for many different cancers. Sequences of proteins expressed by tumors could be used to detect mutations or also the presence of other “non-self proteins” like for example viral antigens, that should be highly represented in hepatitis B virus (HBV)-related HCC (where a high frequency of HBV-DNA integration is known to occur) [9], and target them with T cells expanded from the tumors or engineered to express specific T cell receptors [10].

The experimental framework to translate such knowledge in new therapy has been provided. The realization of clinical benefits for cancer patients might not be such a distant reality.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

References

- [1] Finn OJ. Cancer immunology. N Engl J Med 2008;358:2704–2715.

- [2] Coulie PG, Van den Eynde BJ, Van der Bruggen P, Boon T. Tumor antigens recognized by T lymphocytes: at the core of cancer immunotherapy 2014;14:135–146.
- [3] Morgan RA, Yang JC, Kitano M, Dudley ME, Laurencot CM, Rosenberg SA. Case report of a serious adverse event following the administration of T cells transduced with a chimeric antigen receptor recognizing ERBB2. *Mol Ther* 2010;18:843–851.
- [4] Morgan RA, Chinnasamy N, Abate-daga D, Gros A, Robbins PF, Zheng Z, et al. Cancer regression and neurological toxicity following anti-MAGE-A3 TCR gene therapy. *J Immunother* 2013;36:133–151.
- [5] Linette GP, Stadtmauer EA, Maus MV, Rapoport AP, Levine BL, Emery L, et al. Cardiovascular toxicity and titin cross-reactivity of affinity-enhanced T cells in myeloma and melanoma. *Blood* 2013;122:863–871.
- [6] Rosenberg SA, Yang JC, Robbins PF, Wunderlich JR, Sherry RM, Schwartzentruber DJ, et al. Cell transfer therapy for cancer: lessons from sequential treatments of a patient with metastatic melanoma. *J Immunother* 2003;26:385–393.
- [7] Khong HT, Wang QJ, Rosenberg SA. Identification of multiple antigens recognized by tumor-infiltrating lymphocytes from a single patient: tumor escape by antigen loss and loss of MHC expression. *J Immunol* 2004;27:184–190.
- [8] Kessler JH, Melief CJM. Identification of T-cell epitopes for cancer immunotherapy. *Leukemia* 2007;21:1859–1874.
- [9] Sung W-K, Zheng H, Li S, Chen R, Liu X, Li Y, et al. Genome-wide survey of recurrent HBV integration in hepatocellular carcinoma. *Nat Genet* 2012;44:765–769.
- [10] Koh S, Shimasaki N, Suwanarusk R, Ho ZZ, Chia A, Banu N, et al. A practical approach to immunotherapy of hepatocellular carcinoma using T cells redirected against hepatitis B virus. *Mol Ther Nucleic Acids* 2013;2:e114.

Figure legend

Fig. 1. A schematic of identification of TIL that recognize patient-specific mutation in a patient with epithelial cancer, followed by treatment of patient using adoptive cell therapy with TIL containing V β 22+ *ERBB2IP* mutation-reactive T cells.

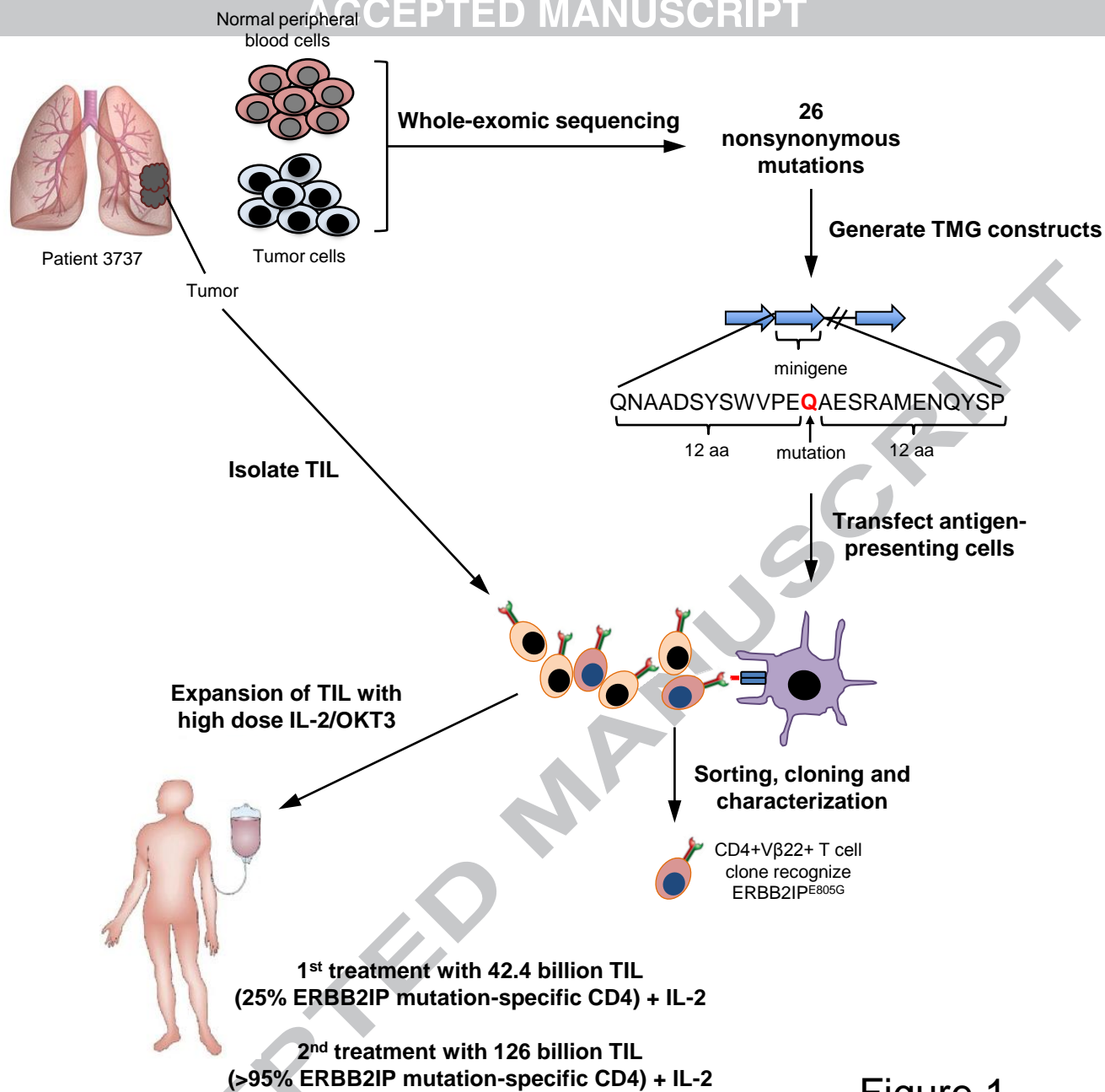


Figure 1